Citation:

Norat T, Bingham S, Ferrari P, Slimani N, Jenab M, Mazuir M, Overvad K, Olsen A, Tjønneland A, Clavel F, Boutron-Ruault C, Kesse E, Boeing H, Bergmann MM, Nieters A, Linseisen J, Trichopoulou A, Trichopoulos D, Tountas Y, Berrino F, Palli D, Panico S, Tunino R, Vineis P, Bas Bueno-de-Mesquita H, Peeters P, Engesset D, Lund E, Skeie G, Ardanaz E, González C, Navarro C, Quirós JR, Sanchez MJ, Berglund G, Mattisson I, Hallmans G, Palmqvist R, Day NE, Khaw KT, Key TJ, San Joaquin M, Hémon B, Saracci R, Kaaks R, Riboli E. Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. J Natl Cancer Inst. 2005 Jun 15;97(12):906-16

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Study Design:

prospective cohort study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To examine assocations between colorectal cancer risk and intakes of red and processed meat, of poultry, and of fish, including different levels of intake of fish and fiber in the European Prospective Investigation into Cancer and Nutrition (EPIC) study.

Inclusion Criteria:

- age: 35 to 70 years between 1992 and 1998

Exclusion Criteria:

- for this analysis:
  - prevalent cancer at enrollment other than nonmelanoma skin cancer
  - in the lowest and highest 1% of the distribution of the ratio of reported total energy intake to energy requirment
  - mssing quesitonnaire data
  - missding dates of diagnosis or follow-up

Description of Study Protocol:

Recruitment

- recruited from general population and resided in defined areas of each country

- in France: women who were members of a health insurance scheme for state school employees
- in Utrecht, The Netherlands: women attending breast cancer screening
- in Italy and Spain: members of local blood donor associations included

Design: prospective cohort study

Blinding used (if applicable): N/A

Intervention (if applicable): N/A

Statistical Analysis:

- Cox regression
- proportional hazard assumption for red meat, fish, and poultry intake in relation to colorecal cancer tested using the likelihood ratio test
  - models compared with and without product terms for red meat and fish variables and follow-up time (years)
- data stratified by center
- primary time variable: age
- covariate: sex
- dietary intake of red meat, processsed meat, poultry and fish: analyzed as continuous variables, and in five cateogries using cut points based on the porgressive doubling of intake levels
  - same cut points applied to each to estimate relative risks
  - categorical variables scored from 1-5
    - trend tests calculated on these scores
    - relative risks calculated from hazard ratio
- results adjusted for estimated energy intake, divided into energy from fat and energy from non-fat sources
- weight and height were adjusted for
- further adustment for : smoking, alcohol intake, dietary fiber, occupational physical activity.
- results were also adjusted for folate intake and use of multivitamin supplements at baseline
- separate analyses done for men and women (adjusted for hormonal replacement therapy)
  - no important differences between sexes, so combined results presented

Data Collection Summary:

Timing of Measurements

dietary intake, demographic, and health data: measured annually between 1992 and 1998

Dependent Variables

- colorectal cancer: cases identfied from population cancer registries, health insurance records, cancer and pathology registries, and active follow-up of study subjects and their next-of-kin

Independent Variables

- dietary intake: country specific validated questionnaires (*an 8% random sample of the cohort provided a second dietary measurement using a very detailed computerized 24-hour diet recall method to calibrate dietary measurements across countries and to correct for systematic over or underestimation of dietary intakes*)

- meats grouped into red meat, processed meat, and poultry
- processed meats: primarilly pork and beef preserved by methods other than freezing - salting (with and without nitrites), smoking, marinating, air drying, or heating i.e. ham, bacon, sausages, blood sausages, meat cuts, "liver pate," salami, bologna, tinned meat, luncheon meat, corned beef, and others
  - *cutpoints for categories of intake of red and processed meats:*
    - low intake: < 30 g/day men; < 13 g/day women
    - medium intake: 30 to 129 g/day men; 13 to 85 g/day women
    - high intake: > 129 g/ men and > 85 g/day women
- poultry: all fresh, frozen, and minced chicken and turkey
- fish: all fresh, canned, salted and smoked fish
  - *cutpoints for categories of intake of fish:*
    - low intake: < 14 g/ day men and women
    - medium intake: 14 to 50 g/day
    - high intake: > 50 g/day

Control Variables

- energy intake (from fat and nonfat sources)
- weight and height
- smoking (never, former, current)
- alcohol intake (grams per day)
- dietary fiber (grams per day)
- occupational physical activity (no activity, sedentary, standing, manual, and heavy manual)
- folate intake in some models
- multivitamin supplements in some models

Description of Actual Data Sample:

Initial N:

- Males: N = 153,457
- Females: N = 366,521

After exclusion criteria applied:

- 22,432 excluded with prevalent cancer at enrollment
- 10,208 excluded in lowest and highest 1% of distribution of ratio of reported total energy intake to energy requirement
- 9298 excluded with missing questionnaire data or missing dates of diagnosis or follow-up
- Final N for this analysis = 478,040

Age: mean (SD)

- Males:
  - Cases (N = 542): 59.6 (7.4) years
  - Noncases (N = 141,445): 52.2 (10.1) years
- Females:
  - Cases (N = 787): 58.7 (7.9) years
  - Noncases (N = 335,265): 50.8 (9.8) years

Ethnicity: 10 different countries in Europe included

Other relevant demographics:

Anthropometrics

Weight (kg)

- Males:
  - Cases: 83.3 (12.6)
  - Noncases: 81.3 (12)
- Females
  - Cases: 67.6 (12.1)
  - Noncases: 66.1 (11.8)

Height (cm)

- Males:
  - Cases: 174.2 (6.8)
  - Noncases: 174.8 (7.4)
- Females:
  - Cases: 161.8 (6.3)
  - Noncases: 162.3 (6.8)

Location: Europe

Summary of Results:

Key Findings:

- Increasing intake of red and processed meat intake was significantly associated with increasing risk of colorectal cancer
- When red meat and processed meat were analyzed separately, only processed meat intake was significantly associated with colorectal cancer
- Intake of fish was significantly inversely associated with colorectal cancer risk
- Intake of poultry was not significantly associated with colorectal cancer risk

Number of diagnoses of colorectal cancer during follow-up - 1,329

- 95% histologically verified
- colon: N = 855
- rectum: N = 474

Red and processed meat intake

- Increasing intake of red and processed meat intake was significantly associated with increasing risk of colorectal cancer for highest versus lowest level of intake
  - HR = 1.57, 95%CI = 1.13 to 2.17, P trend = 0.001 (adjusted for sex and energy intake)
  - after adjustment for other covariates, the increase in risk was reduced:
    - HR = 1.35, 95% CI = 0.96 to 1.88, P trend = 0.03
- red meat and processed meats analyzed separately:
  - red meat intake not significantly associated with colorectal cancer
    - HR for highest versus lowest intake = 1.17, 95% CI: 0.92 TO 1.49, P trend = 0.09

- processed meat intake was signficantly associated with colorectal cancer
    - HR for highest versus lowest intake = 1.42, 95% CI: 1.09 - 1.86, P trend = 0.02
  - results similar for colon and rectum and for right and left side of the colon
- analysis of subgroups of red meats:
  - pork intake significantly associated with colorectal cancer risk:
      - HR for highest versus lowest = 1.18, 95% CI: 0.95 to 1.48, P trend = 0.02
    - after adjustment for intake of the other meats, the trend for increased pork intake remained statistically significant (P trend = 0.03)
  - lamb intake significantly associated with colorectal cancer risk
      - HR = 1.22, 95% CI: 0.96 to 1.55, P trend = 0.03
    - after adjustment for intake of the other meats, N.S
  - beef/veal intake not significantly associated with colorectal cancer risk
      - HR = 1.03, 95% CI: 0.86 to 1.24, P trend = 0.76)
    - after adjustment for intake of the other meats, N.S
  - intakes of ham, bacon, and other processed meats (mainly sausages), were not independently related to colorectal cancer risk
  - positive association of colorectal cancer risk with red and processed meat intake persisted when fish, poultry and red and processed meat were all included as continuous variables in the same model (P trend = 0.02)
  - absolute risk of developing colorectal cancer within 10 years for a study subject aged 50 years was 1.71% for the highest category of red meat inatke and 1.28% for the lowest category of intake
- adjustment for folate intake (in 1176 colorectal cancer case patients, and 407,959 non-cancer patients)
  - results not substantially modified
    - before adjustment, HR for highest vs lowest categories of intake for this group = 1.27, P trend = 0.12
    - after adjustment: HR = 1.25, P trend = 0.15
- exclusion of case patients diagnosed during first 2 years of follow-up did not change results
  - HR for group with highest consumption of red and processed meat
    - before exclusion = 1.35, 05% CI: 0.96 to 1.88 (N=1329 colorectal patients) and
    - after exclusion = 1.35, 95% CI: 0.90 to 2.03 (N=861 colorectal patients)
- calibration of the data for systematic and random dietary intake measurement errors strengthened the observed associations between red and processed meat
  - multivariable HR per 100-gram increase intake of red and processed meat
    - before calibration = 1.25, 95% CI: 1.09 to 1.41, P trend = 0.001
    - after calibration = 1.55, 95% CI: 1.19 to 2.02, P trend = 0.001
  - in corrected models, the association between intake of processed meat was stronger than the association between intake of red meat, but neither association was significant.
  - the corrected estimates for rectal cancer were similar to those for colon cancer
- For centers with more than 50 colorectal cancer cases, the association of red and processed meat intake with colorectal cancer was consistent across centers
- Effect of fiber intake
  - the increase in colorectal cancer risk associated with high intake of red and processed meat was more apparent in those with low (< 17 g/day) and medium (17 to 26 g/day in women and 17 to 28 g/day in men) intakes than in the high intakes (>26 g/day in women and > 28 g/day in men), P interaction = 0.06
    - HR for highest vs lowest intake red/processed meat and
      - high intake fiber = 1.09, 95% CI: 0.83 to 1.42
      - medium intake fiber = 1.20, 95% CI: 0.93 to 1.56

            - low intake of fiber = 1.50, 95% CI: 1.15 to 1.97
        - HR for medium intake red/processed meat and
            - low intake fiber = 1.38, 95% CI: 1.06 to 1.80)
        - the risk reduction associated with high fiber intake was of similar magnitude in all categories of intake of red and processed meat

Fish and poultry intake

- Intake of fish was significantly inversely associated with colorectal cancer risk
    - HR for highest versus lowest category of intake = 0.69, 95% CI: 0.54 to 0.88, P trend < 0.001
    - trend for an inverse association was significant for cancers of the left side of the colon (P trend = 0.02) and for the rectum (P trend < 0.001), but not for cancers of the right side of the colon
- intake of poultry was not significantly associated with colorectal cancer risk
- inverse association of fish intake persisted when fish, poutlry and red and processed meat were all included as continuous variables in the same model (P trend < 0.001)
- absolute risk of developing colorectal cancer within 10 years for a study subject aged 50 years was 1.86% for subjects in the lowest category of fish intake and 1.28% for subjects in the highest category of fish intake
- adjustment for folate intake (in 1176 colorectal cancer case patients, and 407,959 non-cancer patients)
    - results not substantially modified
        - HR for the highest versus the lowest intake of fish
            - before adjustment = 0.68, P trend < 0.001
            - after adjustment = 0.67, P trend < 0.001
- exclusion of case patients diagnosed during first 2 years of follow-up did not change results
    - HR for highest versus lowest intake of fish:
        - before exclusion = 0.69
        - after exclusion = 0.70
- calibration of the data for systematic and random dietary intake measurement errors strengthened the observations between fish intake and colorectal cancer risk
    - HR per 100 gram increase in fish intake
        - before calibration = 0.70, 95% CI: 0.57 to 0.87, P trend < 0.001
        - after calibration = 0.47, 95% CI: 0.27 to 0.77, P trend = .003
    - the association was statistically significant and similar for both colon and rectal cancers
- For centers with more than 50 colorectal cancer case patients, thea association with fish intake was not consistent across centers (P heterogeneity = 0.003)
    - in meta- regression analyses, none of the following independently explained the heterogeneity:
        - geographic regions
        - mean fish intake in each cohort
        - proportion of consumed fish that grilled, fried, or barbecued
        - when mean fatty fish intake from 24-hour dietary recall was included in the models instead of mean total fish intake, results were unchanged.
- displacement of red and processed meat intake by fish
    - no interaction between fish and meat was observed
    - risk increase associated with high consumption of red and processed meat versus low consumption (>129 g/day in men and > 85 g/day in women versus <30 g/day in men and < 13 g/day in women) =~ 12% to 20% independent of the levels of fish

consumption
- risk increase associated with low versus high fish consumption (< 14 g/day in both men and women versus > 50 g/day in mean and women) = ~ 40% independent of the levels of red and processed meat intake.
- high intake red meat and low intake fish compared to low red meat and high fish intake:
    - HR = 1.63, 95% CI: 1.22 to 2.16

Author Conclusion:

Colorectal cancer risk is positively associated with high consumption of red and processed meats and inversely associated with fish consumption and fiber intake.

Reviewer Comments:

The analyses did not adjust for family history of CRC or multiple comparisons.

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes

	2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
	2.2.	Were criteria applied equally to all study groups?	Yes
	2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
	2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**		Yes
	3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
	3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
	3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
	3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
	3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
	3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**		Yes
	4.1.	Were follow-up methods described and the same for all groups?	Yes
	4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
	4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
	4.4.	Were reasons for withdrawals similar across groups?	N/A
	4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**		N/A

	5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
	5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	N/A
	5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
	5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
	5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**		Yes
	6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
	6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
	6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
	6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
	6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
	6.6.	Were extra or unplanned treatments described?	N/A
	6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
	6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**		Yes
	7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
	7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
	7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
	7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
	7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
	7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes

	7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**		Yes
	8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
	8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
	8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
	8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
	8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
	8.6.	Was clinical significance as well as statistical significance reported?	Yes
	8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		Yes
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	Yes